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International application number: PCT/IN04/000447

International filing date: 24 December 2004 (24.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 1210/MUM/2003
Filing date: 24 December 2003 (24.12.2003)

Date of receipt at the International Bureau: 25 May 2005 (25.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS / GEOGRAPHICALINDICATION

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 24/11/2003 and post-dated to 24.12.2003 under Section 17(1) of Patents Act, 1970 in respect of Patent Application No.1210/MUM/2003 of **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI – 400 059, INDIA.**

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

Dated this 16th day of May 2005.

(A. T. PATRE)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA**

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled **"NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT"**

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

TRIPLICATE

We, further declare that the inventors for the said invention are

1) Mr. Natarajan Muthukumaran. 2) Mr. Patel Nileshkumar Sureshbhai. 3) Mr. Bhatt Mehul Chandrakantbhai. 4) Dr. Kilaru Srinivasu 5) Dr.Thennati Rajamannar;

of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-28397632, FACSIMILE NO- 28212110.

1210 | मुंबई MUM | 2003

14 NOV 2003

The application has been post-dated to 24.12.2003, u/s 17(1) of Patents Act, 1970 as amended by Patents (Amendment) Act, 2002.

(R) Jain

C P K. Jain
Exam. of Patents & Designs

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 24th day of November, 2003.

(Signatures) 1. _____
Mr. Natarajan Muthukumaran

2. _____
Mr. Patel Nileshkumar Sureshbhai

3. _____
Mr. Bhatt Mehul Chandrakantbhai

4. _____
Dr. Kilaru Srinivasu

5. _____
Dr.Thennati Rajamannar

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

1) Provisional specification (3 copies)
2) Fee Rs.3000 in cheque bearing No. 435141 dated 21st Nov 2003 on ICICI Bank Ltd.

We request that a patent may be granted to us for the said invention

Dated this 24th day of November, 2003.

(Signature) .....
DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To
The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

ORIGINAL

The following specification describes the nature of this invention

NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

The present invention relates to novel stable polymorphic forms of an anticonvulsant, tiagabine hydrochloride (INN name) used in the treatment of epilepsy.

United States Patent No. 5,010,090 (assigned to Novo Nordisk, referred to hereinafter as **'090**) discloses tiagabine hydrochloride and the process of its preparation. The process adopted herein is very laborious and expensive as it utilizes column chromatography for purification. Further, the product is crystallised using ethyl acetate, isopropanol, acetone or water yielding product contaminated with high levels of solvent. Use of alternative organic solvents such as acetonitrile, butylacetate, toluene, acetone, dichloromethane etc. also gives product containing various amounts of the used crystallization solvent. The crystallization solvents are unwanted as they affect the stability of pharmaceutical products and are toxic to humans. Further the product manufactured using ethylacetate and other organic solvents often forms clathrates, hence not usable as pharmaceutical material due to high levels of solvent contamination. This patent does not disclose the polymorphic form of tiagabine hydrochloride.

United States Patent No. 5,354,760 (assigned to Novo Nordisk, referred to hereinafter as **'760**) discloses crystalline tiagabine hydrochloride as monohydrate referred to herein as form I. This patent provides monohydrate form from water, gives reproducible results, is devoid of solvents and possesses required stability under normal storage conditions, is

non-hygroscopic and is very applicable for pharmaceutical formulations as the only residual solvent in the product is water. However, the monohydrate crystalline form is less stable at elevated temperature making its use inconvenient during formulation.

United States Patent No. 5,958,951 (assigned to Novo Nordisk, referred to hereinafter as **'951**) claims anhydrous crystalline form of tiagabine hydrochloride referred to herein as form II. The product obtained was reported to be non hygroscopic and thermally stable. However, the process for the preparation of anhydrous form is time consuming as it is carried out for about 18 hours.

OBJECT OF THE INVENTION:

The object of the present invention is to provide novel stable forms III and IV of tiagabine hydrochloride.

We have also found novel solvate of tiagabine hydrochloride with acetonitrile.

Yet another object of the present invention is to provide process for the preparation of novel polymorphic forms III, IV, novel solvate with acetonitrile and substantially amorphous form of tiagabine hydrochloride.

DESCRIPTION OF THE INVENTION:

In our attempt to find novel polymorphic forms of tiagabine hydrochloride that are free of entrapped solvents we observed that following the process of tiagabine hydrochloride monohydrate patent i.e. '760 we were not successful in making the claimed monohydrate. On drying the monohydrate to <0.5% water we obtain a product which has x-ray diffraction pattern similar to that reported in '951.

We have found that tiagabine hydrochloride has limited solubility in various organic solvents when compared to that in water. Hence, we resorted to use of solvent(s) to prepare new polymorphs which is advantageous as it results in high yields. The solubility data is given in Table-1.

TABLE-1 : SOLUBILITY DATA OF TIAGABINE HYDROCHLORIDE AT ROOM TEMPERATURE

S.NO	SAMPLE QUANTITY	SOLVENT	VOLUME OF SOLVENT
1	100 mg	Toluene	>100ml
2	100 mg	DMF	0.5 ml
3	100 mg	Ethylacetate	>100 ml
4	100 mg	Acetone	24 ml
5	100 mg	Methanol	0.2 ml
6	100 mg	Ethanol	0.3 ml
7	100 mg	IPA	1.3 ml
8	100 mg	Acetonitrile	>100 ml
9	100 mg	Water	0.7 ml

The novel anhydrous forms III or IV of tiagabine hydrochloride may be prepared by a process comprising dissolving tiagabine hydrochloride in solvent(s) followed by crystallizing tiagabine hydrochloride from the abovementioned solvent(s). Crystallization may be achieved by dissolving tiagabine hydrochloride in a solvent followed by cooling or by addition of non-solvent or by distilling off the solvent in the presence or absence of vacuum. The process of crystallization may be carried out with or without the presence of seed crystals.

The solvent(s) may be selected from the group consisting of aliphatic or aromatic or cyclic hydrocarbon such as n-pentane, n-hexane, n-octane, cyclohexane, toluene and the

like; halogenated aliphatic or aromatic hydrocarbons such as dichloromethane, chlorobenzene; alkanols such as methanol, ethanol, t-butanol, isopropanol, cyclohexanol and the like; ethers such as diethylether, tetrahydrofuran, dioxane; ketones such as acetone, methylethylketone, cyclohexanone; nitriles such as acetonitrile; amides such as dimethylformamide, dimethylacetamide and the like; esters such as ethylacetate, butylacetate ; sulfoxides such as dimethylsulfoxide and the like; water and mixtures thereof.

The dissolution of tiagabine hydrochloride in solvent(s) may be carried out at ambient or at elevated temperatures.

Crystallization of tiagabine hydrochloride from the solution may be carried out at ambient or lower temperatures. Crystallization may be allowed to occur by chilling or seeding or scratching the glass of the reaction vessel or cooling and other such common techniques.

Isolation of the novel polymorphic forms may be achieved by using standard techniques known to those skilled in the art such as filtration/centrifugation and drying. Filtration may be carried out in the presence or absence of vacuum. Drying may be carried out at ambient or elevated temperature in the presence or absence of vacuum. The product may be dried using different techniques of drying like fluid bed drying, tray drying, spray freeze drying and rotatory drying techniques with or without application of vacuum and / or under inert conditions.

The novel stable forms III and IV are characterized by x-ray powder diffractograms as represented in figs 1 & 2.

The novel solvate of tiagabine hydrochloride with acetonitrile is characterized by x-ray powder diffractogram as represented in fig. 3. The novel solvate of tiagabine hydrochloride with acetonitrile is found to be stable and isolable in good yields.

The new polymorphic forms are suitable for pharmaceutical formulations.

We have also found that the solvates of tiagabine hydrochloride can also be employed for making the new forms for eg. stable acetonitrile solvate having 1 mole of acetonitrile when dried at 85-90^{0}C under vacuum yields form III of tiagabine hydrochloride.

The forms thus obtained from organic solvents or from drying of the solvates had solvent levels below the acceptable limits, meeting ICH requirements. The data was reported in Table-2.

TABLE-2 : RESIDUAL SOLVENT DATA

S.no.	Exp. No.	Solvent(s) used for crystallization	Solvent content	Limits as per ICH
1.	630/12	DMF + TOLUENE	Not detected Not detected	NMT 880 ppm NMT 890 ppm
2	630/16	DMF + TOLUENE	Not detected 3 ppm	NMT 880 ppm NMT 890 ppm
2.	$630/37_a$	ETHYLACETATE	Not detected	NMT 5000 ppm
3.	$630/37_b$	ISOPROPANOL	10 ppm	NMT 5000 ppm
4.	$630/37_c$	ACETONE	556 ppm	NMT 5000 ppm
5.	616/20B	METHANOL+ THF	Not detected 05	NMT 3000 ppm NMT 720 ppm
6	641/04a	ACETONITRILE	Not detected	NMT 410 ppm

The invention is further illustrated but not restricted by the description in the following examples.

EXAMPLES

Example 1 : Form –III of tiagabine hydrochloride

66 gm of tiagabine hydrochloride is dissolved in 135 ml DMF at 60-70^{0}C and the solution filtered. 1200 ml toluene is added to DMF solution containing tiagabine hydrochloride at 50-55^{0}C for a period of 15 min and the mixture is gradually cooled to room temperature in 1 hr period and further cooled to 0-5^{0}C and maintained at 0-5^{0}C for 1.5 hr. The material is filtered and washed with 150 ml toluene. Dried the material at 50-55 ^{0}C till LOD comes to less than 0.5%.

Example 2 : Form-IV of tiagabine hydrochloride

650 gm of tiagabine hydrochloride is dissolved in 1.5 lit DMF at 70-80^{0}C, and added to 6.5 lit toluene at room temperature for a period of 30 min and the mixture is gradually cooled to room temperature in 30 min time and further cooled to 5-10^{0}C in 30 min time and maintained at 5-10^{0}C for 2 hrs. The material is filtered and washed with 1.3 lit toluene. Dried the material at 55-58 ^{0}C till LOD comes to less than 0.5%.

(LOD Result 0.1%)

Example 3 : Amorphous form of tiagabine hydrochloride

25 gm tiagabine hydrochloride is dissolved in 125 ml methanol + water mixture in 1:1 ratio at room temperature and spray dried the material at 45-50^{0}C . It can also be prepared by dissolving 25 gm tiagabine hydrochloride in 175 ml water at 50-55^{0}C temperature and spray dried the material at 60^{0}C. Another method of preparing amorphous form is by

dissolving 10 gm tiagabine hydrochloride in 110 ml distilled water at room temperature and freeze dried the material for 24 hrs.

Example 4 : Monoacetonitrile solvate of tiagabine hydrochloride

5 gm of tiagabine hydrochloride is dissolved in 5 ml of methanol at 50-55^{0}C, 50 ml acetonitrile is added to the methanol solution at 40-55^{0}C and cooled to room temperature in 1 hr period and further cooled to 5-10^{0}C and stirred for 2 hrs. Allowed the product to settle down and decanted the clear liquid. 50 ml ethyl acetate is added to the solid mass and stirred at 5-10^{0}C for 30 min, allowed the product to settle down the and decanted the clear liquid. Once again 50 ml ethyl acetate is added to the solid mass and stirred at 5-10^{0}C for 30 min, allowed the product to settle down the and decanted the clear liquid and dried the rpoduct mass in rotavapour under mild vaccum at 50^{0}C for 2hrs.

The obtained acetonitrile solvate form was dried at 85-90^{0}C under vacuum to obtain form – III of tiagabine hydrochloride.

Dated this 24th November 2003

DILIP SHANGHVI

CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED

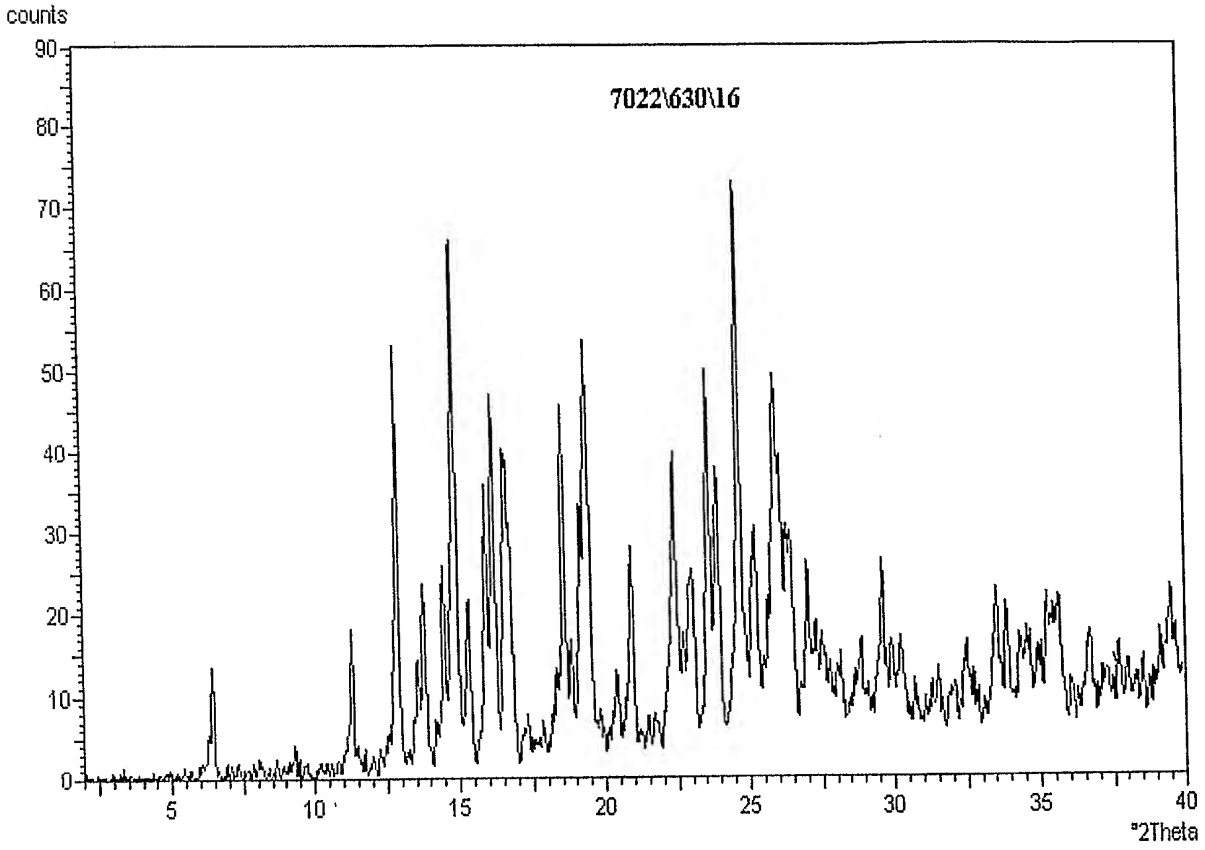

Fig. 1 : XRD PATTERN OF FORM III

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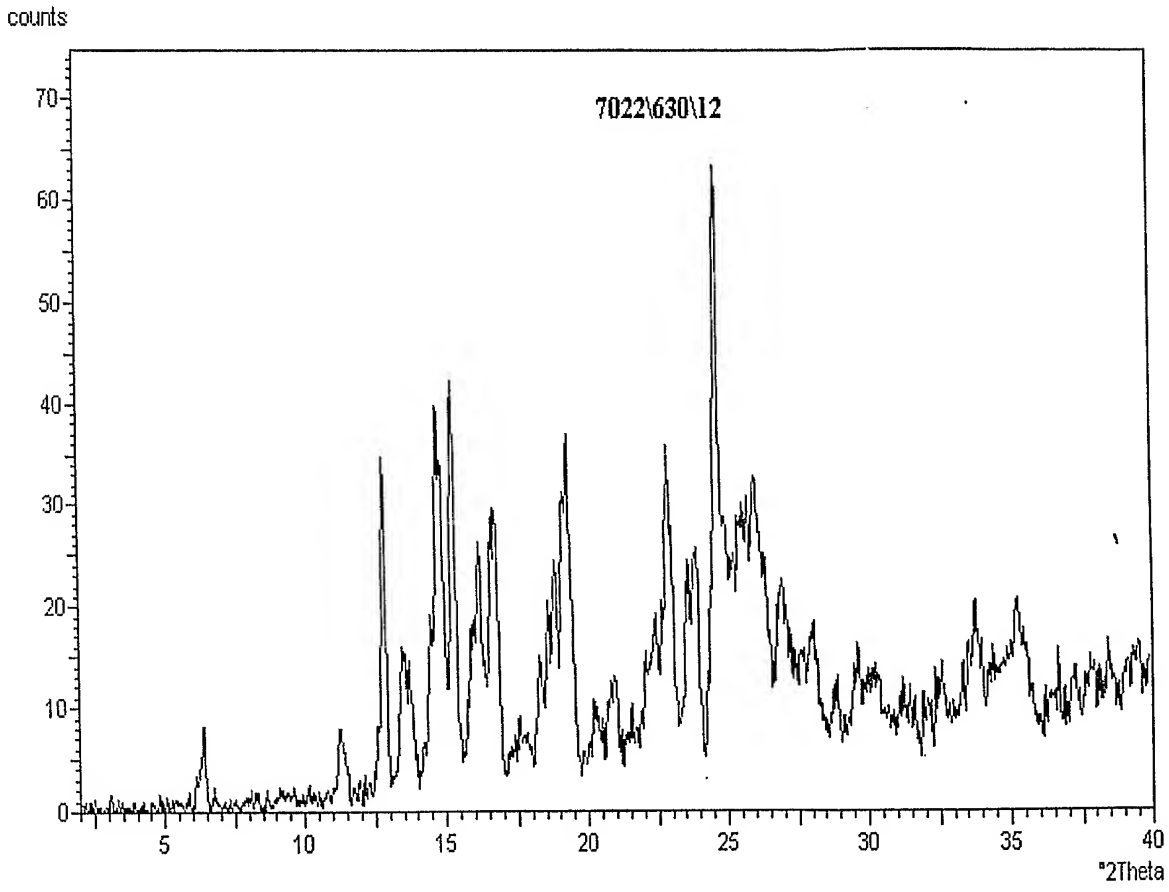

Fig. 2 : XRD PATTERN OF FORM IV

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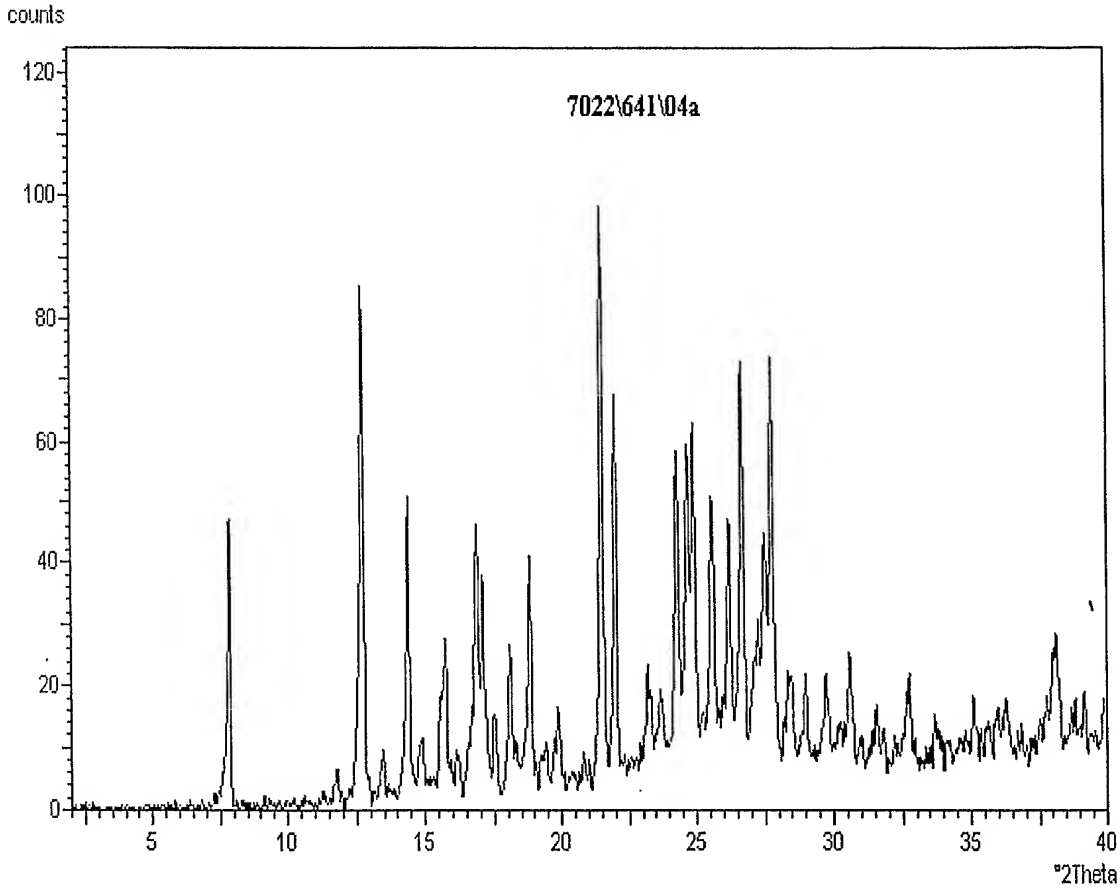

Fig.3: XRD PATTERN OF ACETONITRILE SOLVATE FORM

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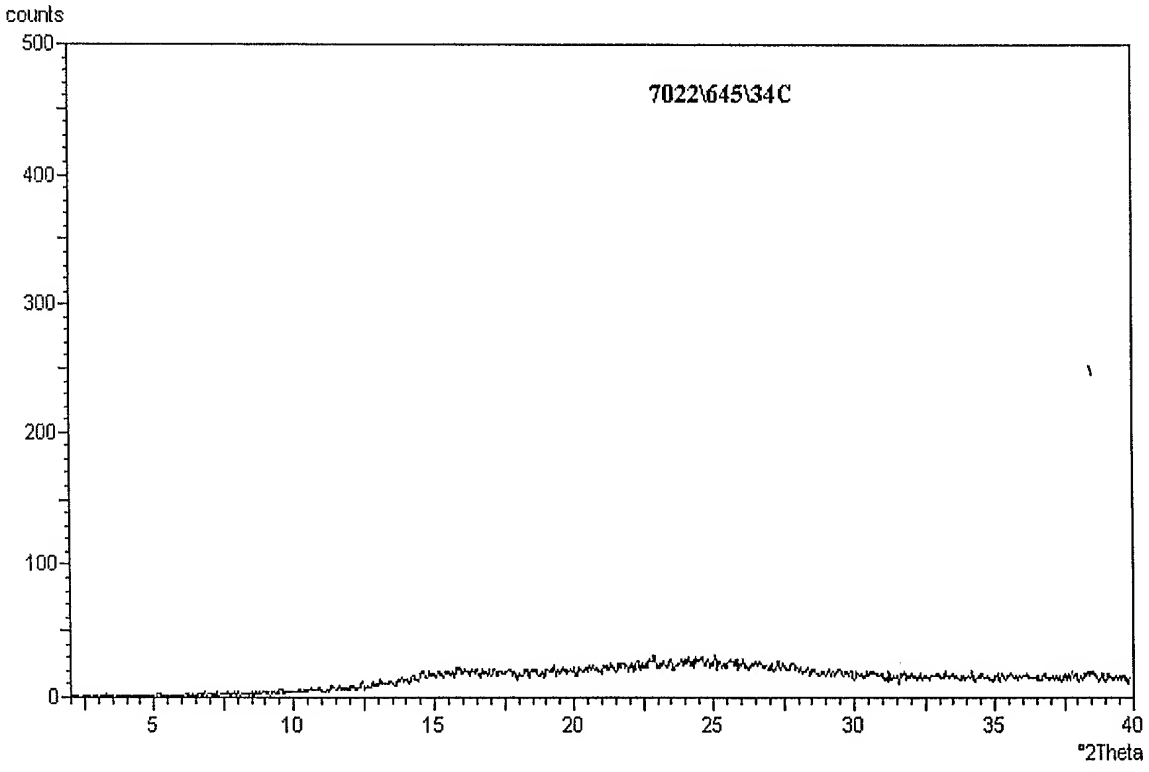

Fig. 4 : XRD PATTERN OF FORM V AMORPHOUS FORM (Prepared by spray drying method)

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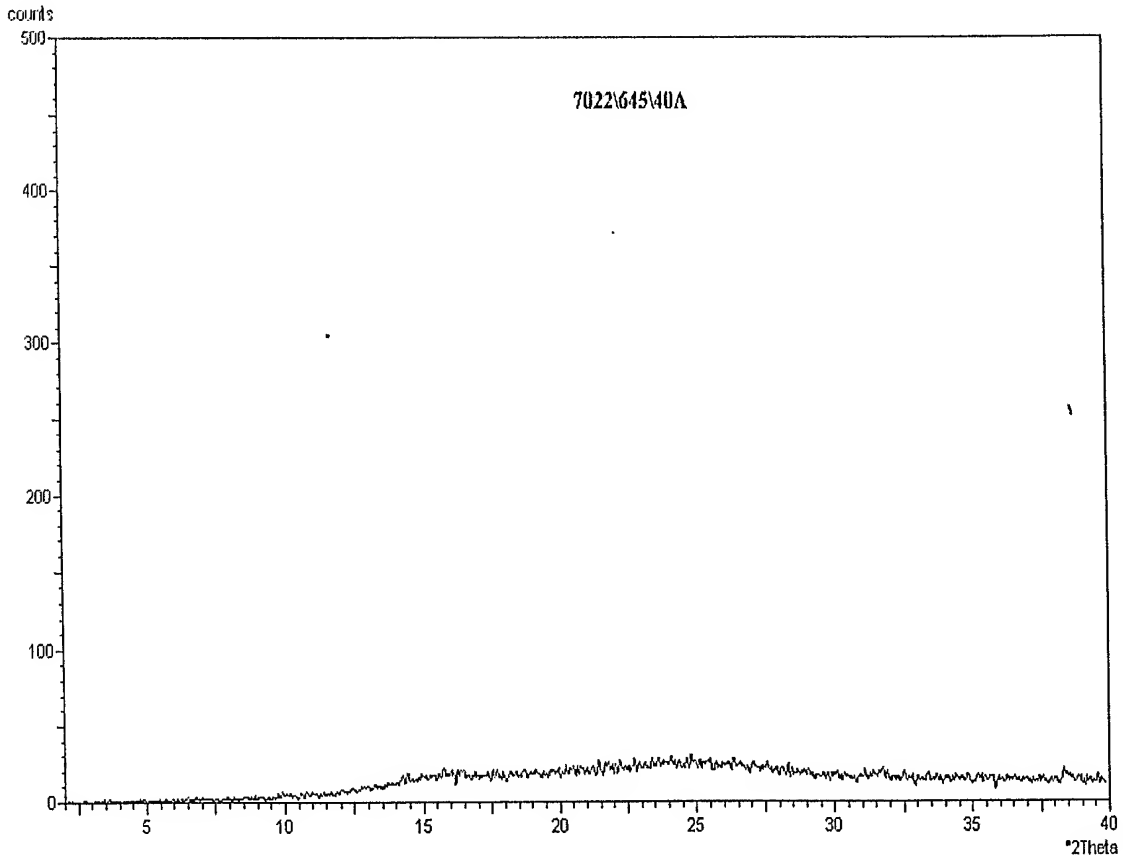

Fig. 5 : XRD PATTERN OF FORM V AMORPHOUS FORM (Prepared by freeze drying method)

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